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10/518,559	12/21/2004	Tadashi Okamoto	1232-5564	8048

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EXAMINER	
BHAT, NARAYAN KAMESHWAR	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/518,559	OKAMOTO, TADASHI	
	Examiner	Art Unit	
	NARAYAN K. BHAT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-29 and 32-38* is/are pending in the application.

4a) Of the above claim(s) *12,16-23,25,26 and 36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This office action is written in reply to applicant's correspondence filed April 21, 2008. **THIS ACTION IS MADE FINAL.**

2. Claims 1-5, 8-29 and 32-38 are pending in this application.

3. Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 are under prosecution.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Donnell et al (WO 98/20020 published May 14, 1998) in view of Heckman et al (USPN 6,124,099 issued September 26, 2000) and further in view of Marriott et al (Biochemistry international, 1992, 26, 943-951, cited in the IDS of the instant invention).

Previous rejections are maintained.

Regarding claim 1, O'Donnell et al teaches a method of acquiring data on the mass of a substance fixed on a solid substrate (pg.7, lines 1-6), that includes immobilizing nucleic acids on the substrate using photo cleavable linker moiety (pg. 33, lines 12-17), thus teaching a structure including a partial structure to be disconnected by

light to fix the substance on the substrate (pg. 33, 18-23); irradiating the substance fixed on the substrate with a laser (pg. 34, lines 26-28), which is light for inducing the disconnection of the partial structure to be disconnected by light; and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (Fig. 17, pg. 25 lines 7-29).

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light, which meet the limitation of the claim. Heckman et al also teaches that the linker

represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photoclevage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photoclevage of the photocross linked biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of

nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12), thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 2, O'Donnell et al teaches a method that include a means of analyzing the mass spectrum is matrix assisted laser desorption ionization time-of-flight mass spectrometry (pg. 49, lines 17-22).

Regarding claim 3, O'Donnell et al teaches a laser, i.e., light for inducing the disconnection of the partial structure to be disconnected by light is a laser beam used for the analysis by MALDI-TOF MS (pg. 34, lines 26-28).

Regarding claim 4, O'Donnell et al teaches that the laser beam used for the analysis by MALDI-TOF MS is a nitrogen laser beam (pg. 73, line 7).

Regarding claim 5, O'Donnell et al teaches that the substance fixed on the substrate is nucleic acid (pg. 72, lines 20-22).

Regarding claim 8, O'Donnell et al teaches a substrate is a glass substrate (Fig. 7, Step1, pg. 49, lines 1-5) having a primary amino group formed on the surface (Fig. 7, step 2), a thiol (SH) group is bonded to the terminal of the nucleic acid substance, and the amino group and the thiol group are bonded together by a compound (Fig. 7, step 3). O'Donnell teaches different type of linkers including the SIAB linker and 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, and pgs. 38-47) photocleavable linker to

couple the nucleic acid substance to the substrate. Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the amino group and the succinimide ester site of the compound and a reaction between the thiol group and the bromobenzyl site of the compound.

Regarding claim 9, O'Donnell et al teaches the formation of a primary amino group on the glass substrate is carried out by using a silane coupling agent having the primary amino group (Fig. 7, pg. 23, lines 14-19).

Regarding claim 10, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13) and further teaches sulfanil group formed on the surface by bonding of an amino group on the terminal of the substance, and the thiol group on the substrate (pgs. 64 and 65, lines 24-29 and 1-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the thiol group and the bromobenzyl site of the compound and a reaction between the amino group and the succinimide ester site of the compound.

Regarding claim 11, O'Donnell et al in view of Heckman et al teaches the formation of a thiol group on the glass substrate is carried out by using a silane coupling agent having the thiol group (pg. 65, lines 11-13).

Regarding claim 13, O'Donnell et al teaches a substance (matrix substance) for assisting the desorption and ionization of the substance fixed on the substrate is applied to at least a region to be used for the mass spectrometry of the substrate (pg.81, lines 25-29).

Regarding claim 14, O'Donnell et al teaches the thickness of the coating film of the matrix substance is large enough and required for the desorption and ionization of the substance fixed on the substrate (Fig. 12, pg. 85, lines 20-29).

Regarding claim 15, O'Donnell et al a method of acquiring data on the mass of a nucleic acid, i.e., bio-related substance on each matrix of a biochip having a plurality of bio-related substances fixed on a substrate in a matrix form by a structure including a partial structure to be disconnected by light, the method comprising the steps of immobilizing nucleic acids on the substrate in a matrix form (Fig. 14, pg. 24, lines 21-27), using photo cleavable linker moiety (pg. 33, lines 12-17) and further teaches irradiating the bio-related substance on each matrix fixed on the substrate with a laser (pg. 34, lines 26-28), which is light for inducing the disconnection of the partial structure to be disconnected by light; and analyzing the mass spectrum of the substance which is brought in an unfixed state by disconnecting the partial structure by the irradiation of light (Fig. 17, pg. 25 lines 7-29).

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light, which meet the limitation of the claim. Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of

O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photoclevage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photoclevage of the photocross linked biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12), thus enhancing

the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 24, O'Donnell et al teaches method of acquiring data on the mass of a nucleic acid, i.e., a bio-related substance on each matrix of a biochip having a plurality of bio-related substances fixed on a substrate in a matrix form and the mass of a substance which interacts with the bio-related substance, the method comprising the steps of: fixing the bio-related substance on each matrix on the substrate (Fig. 14, pg. 24, lines 21-27) by photo cleavable linker (pg. 33, lines 12-17), that is a structure including a partial structure to be disconnected by light; placing the substance which interacts with the bio-related substance on each matrix of the biochip under an interactive condition (pg. 81, lines 25-29; See the entire sample preparation and dispensing section); irradiating the bio-related substance fixed on the substrate with a laser (pg. 34, lines 26-28), that is a light for inducing the disconnection of the partial structure to be disconnected by light; and analyzing the mass spectra of the bio-related substance which has been brought in an unfixed state by the irradiation of light and the substance which has interacted with the bio-related substance in an unfixed state at the same time by disconnecting the partial structure (Figs. 16-18, pg. 25, lines 7-29; Example 5).

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a

photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light, which meet the limitation of the claim. Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in

the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photoclevage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photoclevage of the photocross linked biomolecules of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12), thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 27, O'Donnell et al teaches a method of determining a base sequence of nucleic acid, comprising the steps of: (1) fixing, to a substrate, nucleic acid (DNA) complementary to a part or an entire part of a base sequence on a 3'-side from a

site desired for analysis of a base sequence of nucleic acid (DNA) desired for analysis of the base sequence as a primer used for performing an enzymatic nucleic acid extension reaction, using the nucleic acid desired for analysis of the base sequence as a template, in a structure containing a partial structure to be disconnected by light on a 5'-side from the complimentary base sequence in the primer (Figs. 18 and 19, pg. 25 and 26, lines 24-29 and 1-22); (2) annealing the nucleic acid desired for analysis of the base sequence to the primer fixed to the substrate at the complementary base sequence portion to form a hybrid (Fig. 18, top left panel) ; (3) performing the enzymatic extension reaction using the nucleic acid desired for analysis of the base sequence as a template, on the substrate where the hybrid is formed, in the presence of appropriate amounts of 4 kinds of 2'-deoxynucleotide triphosphate (dNTP: N is A; adenine, G; guanine, C; cytosine, T; thymine) required for the enzymatic nucleic acid extension reaction and the 4 kinds of 2',3'-dideoxynucleotide triphosphate (ddNTP) as a terminator for an extension reaction (Fig. 18, Top left panel, see the step probe with ddT, pg. 26, lines 1-8)

O'Donnell et al also teaches removing the template nucleic acid from the substrate where the extension reaction is effected (pg. 37, lines 1-20, step 4 of the said claim) and further teaches irradiating a plurality of extension reaction products having different chain lengths including a primer portion fixed to the substrate (Fig. 19).

O'Donnell et al also teaches photo cleavable linker moiety (pg. 33, lines 12-17) that is a structure containing a partial structure to be disconnected by a laser (pg. 34, lines 26-28), that is light, for disconnecting the partial structure to be disconnected,

analyzing a molecular weight of the extension product disconnected by the irradiation with light by a MALDI-TOF MS method, and clarifying a base sequence of an extension portion of the extension product based on an increase in a molecular weight from a molecular weight of the primer in the extension product (Fig. 20, pg. 26, lines 24-29, step 5 of the said claim ; and (6) analyzing a part or an entire part of the base sequence desired for analysis of nucleic acid desired for analysis of the base sequence, based on the base sequence of the extension portion (Example 6 and 7, pg. 91-93) .

O'Donnell et al also teaches an exemplary photocleavable linker include 3-amino-(2-nitrophenyl) propionic acid (pg. 33, line 15, pgs. 38-47), which has the structure containing nitrobenzene and further teaches that the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9), thus teaching nitrobenzene is the selected partial structure to be disconnected by the irradiation of light.

O'Donnell et al do not teach the structure containing nitrobenzene is constructed with a compound represented by formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (see instant specification paragraph 0115). However a structure containing formula II, i.e., succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate was known in the art at the time of the claimed invention as taught by Heckman et al.

Heckman et al teaches a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). It is noted that the linker taught by Heckman et al is a photoactive cross linking agent, however, it is incorporated in to nucleic acid molecule (column 3, lines 19-29), which is a partial structure that responds to light,

which meet the limitation of the claim. Heckman et al also teaches that the linker represented by formula II, attaches to the nucleic acid via covalent linkage and has very high long term stability in the dark (column 8, lines 21-27).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to include the a linker -succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate of Heckman et al as an additional linker in the method of O'Donnell et al with the expected benefit of incorporating linker forming a covalent bond with a long term stability as taught by Heckman et al (column 8, lines 21-27).

O'Donnell et al in view of Heckman et al do not teach a photo cross-linking agent is also photocleavable. However light mediated chemical bond cleavage was known in the art at the time of the claimed invention was made as taught by Marriott et al who teaches 4-bromomethyl-3-nitrobenzoic acid succinimide ester to cross link F-actin, a biomolecule (Fig. 1a and b, pg. 944, paragraphs 3-6) and further teaches photoclevage of the cross linked biomolecules (pg. 944, paragraph 7). Marriott et al also teaches that light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and further teaches the dissociation of the macromolecular complex through thioether linkage (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12).

It would be obvious to one having the ordinary skill in the art at the time the invention was made to modify the method of using Formula II linker of O'Donnell et al in view of Heckman et al and use the photoclevage of the photocross linked biomolecules

of Marriott et al with the expected benefit of light mediated chemical bond cleavage of nitrobenzyl derivative of biomolecules, which provides a simple and effective method to generate concentration jumps of substrates and ligands in complex biological medium and to dissociate the macromolecular complex as taught by Marriott et al (Fig. 1b, Fig. 3a, pgs. 943, 944 and 948, paragraphs 1,1 and 1; pg. 948 lines 1-12), thus enhancing the utilities of the formula II linker in the method of acquiring data from mass of the substance.

Regarding claim 28, O'Donnell et al teaches a laser, i.e., light for inducing the disconnection of the partial structure to be disconnected by light is a laser beam used for the analysis by MALDI-TOF MS (pg. 34, lines 26-28),

Regarding claim 29, O'Donnell et al teaches that the laser beam used for the analysis by MALDI-TOF MS is a nitrogen laser beam (pg. 73, line 7).

Regarding claim 32, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13) and further teaches sulfanil group formed on the surface by bonding of an amino group on the terminal of the substance, and the thiol group on the substrate (pgs. 64 and 65, lines 24-29 and 1-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the thiol

group and the bromobenzyl site of the compound and a reaction between the amino group and the succinimide ester site of the compound.

Regarding claim 33, O'Donnell et al in view of Heckman et al teaches the formation of a primary amino group on the glass substrate is carried out by using a silane coupling agent having the primary amino group (Fig. 7, pg. 23, lines 14-19).

Regarding claim 34, O'Donnell et al teaches a substrate is a glass substrate (pg. 49, lines 1-5) having a silane coupling agent having thiol group (pg. 65, lines 11-13) and further teaches sulfanil group formed on the surface by bonding of an amino group on the terminal of the substance, and the thiol group on the substrate (pgs. 64 and 65, lines 24-29 and 1-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a reaction between the thiol group and the bromobenzyl site of the compound and a reaction between the amino group and the succinimide ester site of the compound.

Regarding claim 35, O'Donnell et al in view of Heckman et al teaches that a sulfanil group is formed on the glass substrate by using a silane coupling agent having a sulfanil group (Fig. 7, last step, pg. 65, lines 5-27). Heckman et al teaches succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate (column 3, lines15-16). Marriott et al teaches the BNBA-SE and nitrobenzyl group containing linker to crosslink actin molecules through amine and thio groups (Fig. 1a and b). The combined teachings of

O'Donnell et al, Heckman et al and Marriott et al provides an embodiment which provides a sulfanil group formed on the glass substrate by using a silane coupling agent having a sulfanil group.

Regarding claim 37, O'Donnell et al teaches a Thermo sequenase, an enzyme used for the extension reaction has heat resisting property (Fig. 19, pg. 92, lines1-3).

Regarding claim 38, O'Donnell et al teaches a method wherein the substrate to which the primer is fixed is in a form of a nucleic acid chip in which a plurality of primer nucleic acids are placed in a matrix in the process (Fig. 19, pg. 83, lines 1-15) a part or an entire part of the primer nucleic acid is subjected to an enzymatic nucleic acid extension reaction together with the template thereof on the nucleic acid chip, and in the process (4), the matrix portion subjected to the extension reaction is analyzed by the MALDI-TOF MS method (pg. 83, lines 16-24).

Response to remarks from the Applicants

Rejections under 35 U.S.C. § 103(a)

6. Applicant's arguments with respect to claims 1-5, 8-11, 13-15, 24, 27-29, 32-35 and 37-38 as being unpatentable over O'Donnell et al in view of Heckman et al and further in view of Marriott et al filed on April 21, 2008, have been fully considered but are not persuasive for the following reasons.

Applicant's acknowledgement of teachings of O'Donnell et al directed to a process for immobilizing high density nucleic acids on an insoluble surface for mass spectrometric detection of nucleic acids is duly noted (Remarks, pg. 3, paragraph 2).

Applicant's acknowledgement of teachings of Heckman et al directed to succinimidyl 6-(4-bromomethyl-3-nitrobenzoyl) aminohexanoate compound within the scope of Formula II is also duly noted (Remarks, pg. 4, paragraph 2).

In response to Applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As described in this office action in detail in section 5, O'Donnell et al teaches all the recited steps in the independent claims 1, 15, 24 and 27, including the nitrobenzyl group as a photocleavable group (pg. 34, lines 3-9) except for the nitrobenzene derivative represented by the formula II, which is taught by Heckman et al (column 3, lines 15-16). The photoclevage of the nitrobenzyl derivative crosslinker type is taught by Marriott et al (Fig. 1a and b, pg. 944, paragraphs 3). Applicant has not traversed or addressed the motivation provided in the previous office action to combine the teachings of Heckman et al, O'Donnell et al and Marriott et al.

Applicant argues that "Heckman fails to teach the succinimidyl 6-[4-bromomethyl-3-nitrobenzoyl] aminohexanoate linker as a bifunctional linker to connect a substance to the substrate" (Remarks, pg. 4, paragraph 2). This argument is not persuasive.

As Applicant notes, Heckman et al teaches the succinimidyl 6-[4-bromomethyl-3-nitrobenzoyl] aminohexanoate linker encompassed by formula II. Applicant's arguments regarding bifunctional linker not taught by Heckman et al are irrelevant in view of two facts: 1. "bifunctional linker" is not required by the claim. 2. Heckman et al teaches the

succinimidyl 6-[4-bromomethyl-3-nitrobenzoyl] aminohexanoate linker encompassed by formula II. Furthermore, as cited in this office action in section 5, succinimidyl 6-[4-bromomethyl-3-nitrobenzoyl] aminohexanoate linker taught by Heckman et al is very stable (column 8, lines 21-27). Therefore one would have preferred to use the succinimidyl 6-[4-bromomethyl-3-nitrobenzoyl] aminohexanoate linker based on known stability.

Applicant argues that "wouldn't have a reasonable expectation of success" (Remarks, pg. 5, paragraph 1). This argument is not persuasive because Applicant has not provided any evidence why the linker of Heckman won't work when combined with the method of O'Donnell. Furthermore, Applicants have not traversed or addressed the motivation to combine the teachings of Heckman and Marriott. As described in this office action in detail in section 5, the formula II linker not taught by O'Donnell et al, is taught by Heckman et al and provides motivation to combine with the method of O'Donnell et al for its long term stability (See office action pg. 4, paragraph 2). O'Donnell and Heckman do not teach photoclevage of the formula II linker, which is taught by Marriott and provides motivation to combine with the method of O'Donnell and Heckman for effectively releasing the coupled compound to increase its concentration (see the office action, pg. 5, paragraph 3).

Conclusion

7. No claims are allowed.

8. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

Narayan K. Bhat, Ph. D.

/BJ Forman/

Primary Examiner, Art Unit 1634